METABOLIC PATHWAY ANALYSIS

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Inferring optimal minimal medium on genome-scale metabolic models using evolutionary algorithms

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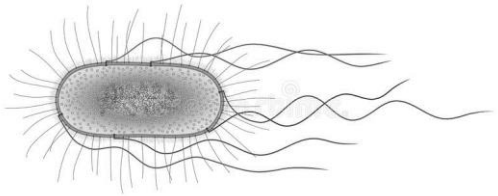
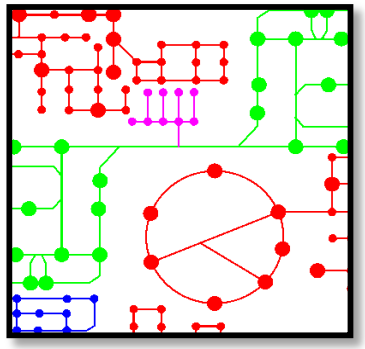
Introduction

Genome Scale Metabolic Models





Phenotypic states

Environmental

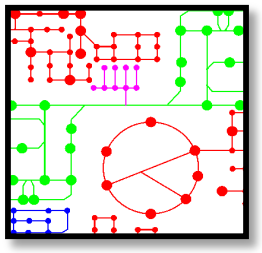
Genetic

Metabolic Engineering Strategies

Information

- ✓ Biochemical data
- ✓ Biomass composition data
- ✓ Medium Composition
- ✓ Experimental data

Objective

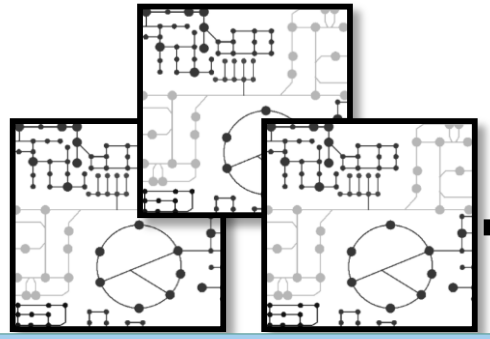


Single Organisms

Optimization

Producing desired compounds

- ✓ Genetic manipulation
- ✓ Medium manipulation
- ✓ Community manipulation



Optimization

Producing desired compounds

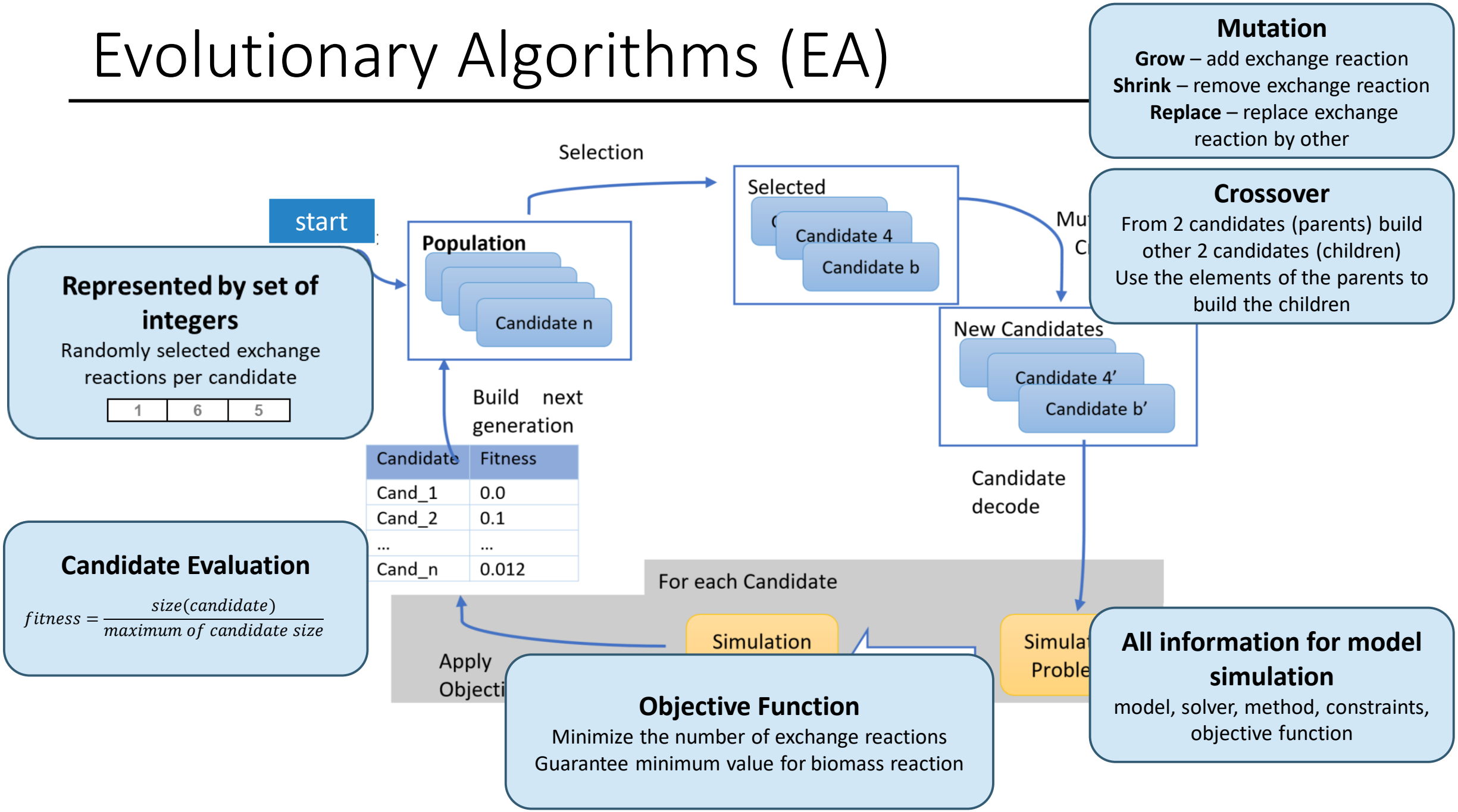
Use evolutionary algorithms to predict optimal minimal medium on genome-scale metabolic models

OptimModels Framework

- Analysis, Simulation and Optimization of **Stoichiometric**, Dynamic and Gecko models;
- Fully implemented in Python language;
- Uses three other open sources Python frameworks:
  - **FRAMED:** analysis and simulation of metabolic models in SBML format;
  - **Odespy:** solve systems of ordinary differential equations (ODEs);
  - **Inspyred:** create biologically-inspired computational intelligence algorithms, including evolutionary computation
- Code, installation files and documentation are available at the GitHub repository

https://github.com/BioSystemsUM/optimModels

Evolutionary Algorithms (EA)



Experimental Setup

Models	Published GSMMS in SBML format, manually curated with minimal medium experimental data available	98 organisms (22 communities)
Solver	CPLEX version 12.8.0.0 - Academic license	
Method	Parsimonius Flux Balance Analysis (pFBA)	
Constraints	Minimum of 10% of the value of biomass reaction One carbon source as input (example: glucose)	
Objective Function	Minimize the number of open exchange reactions	

All solutions with highest score were analyzed

Results

Single Organisms

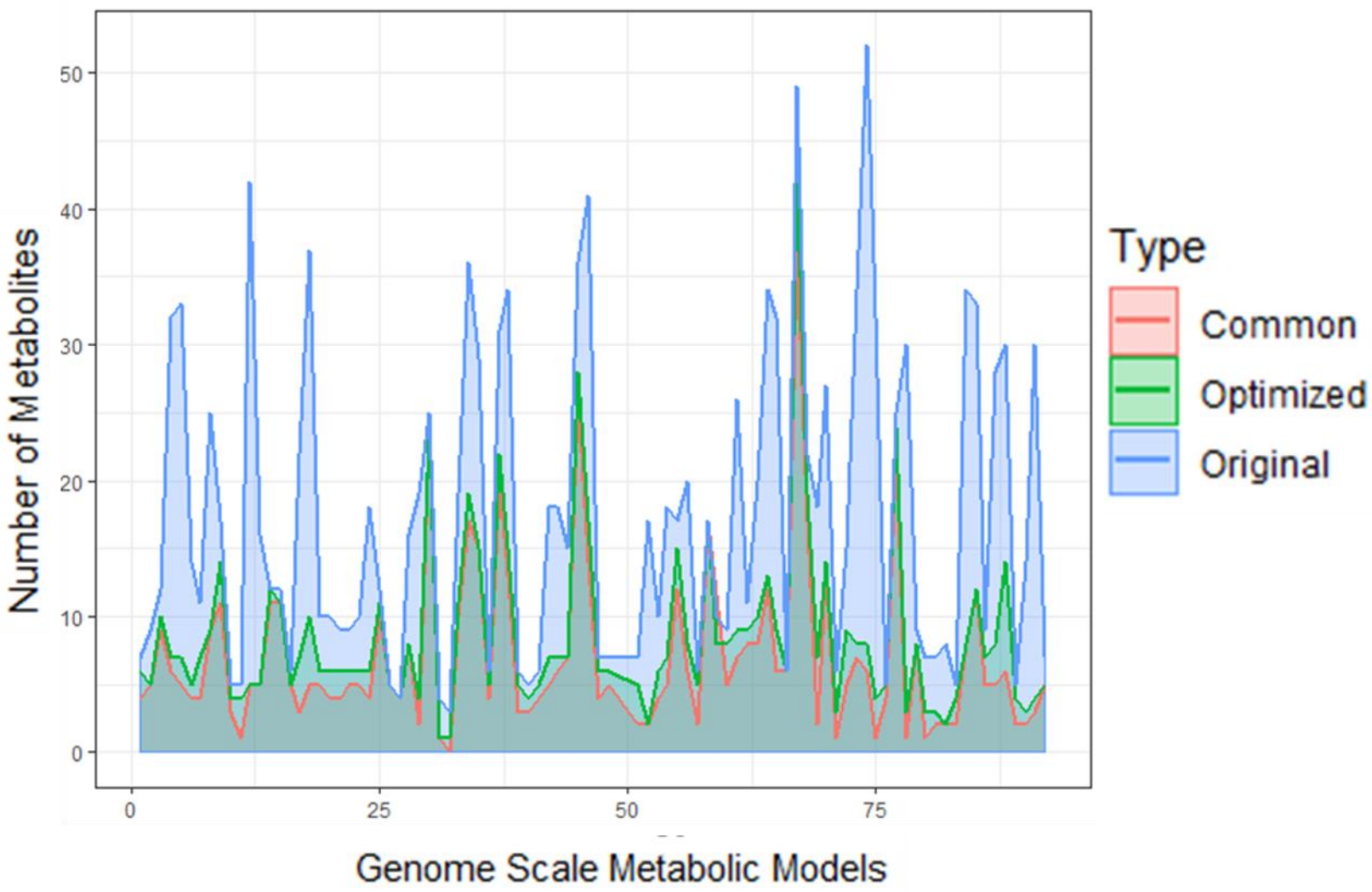
Results

Minimal Medium Composition Comparison

Optimized minimal medium **(green)** is reduced in all cases comparing with original medium **(blue)**

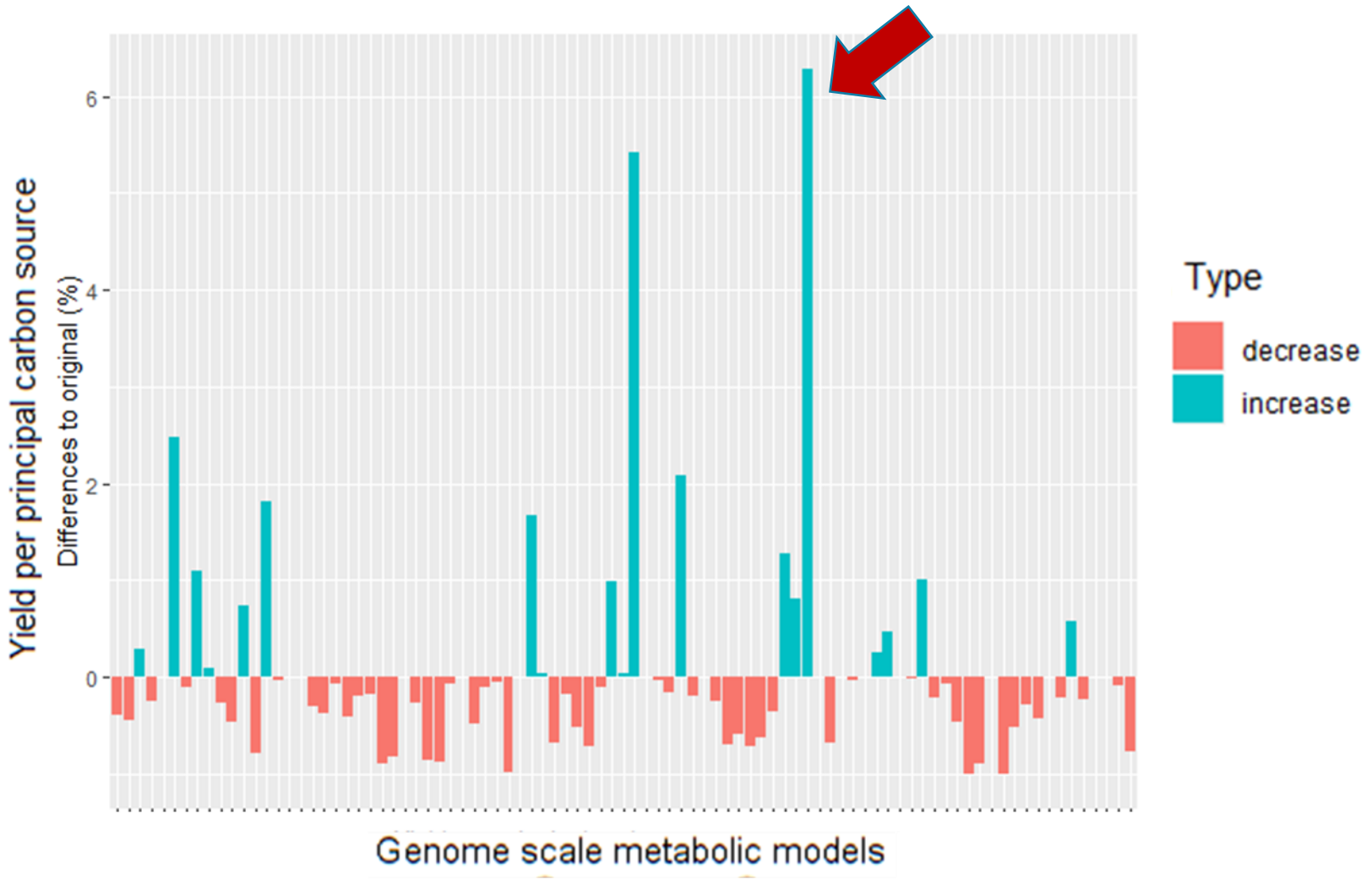
Most of the metabolites in the optimized medium are in common **(red)** with the original medium

Differences in the compositions are due to the algorithm selection of different nitrogen, sulfur and phosphate sources. (example: sulfate - cysteine)



Results

Biomass Yield per Carbon Source Comparison



pFBA simulation was preformed using the **original** and **optimized medium**

Exchange reactions constraints were **maintained for common and original metabolites** and for new ones **the lower bound was set at-10**

The biomass yield per principal carbon source is in general lower when optimized minimal medium is used as input

High yield values are due to metabolites that can be used as both carbon source and ammonia, sulfur or phosphate

Results

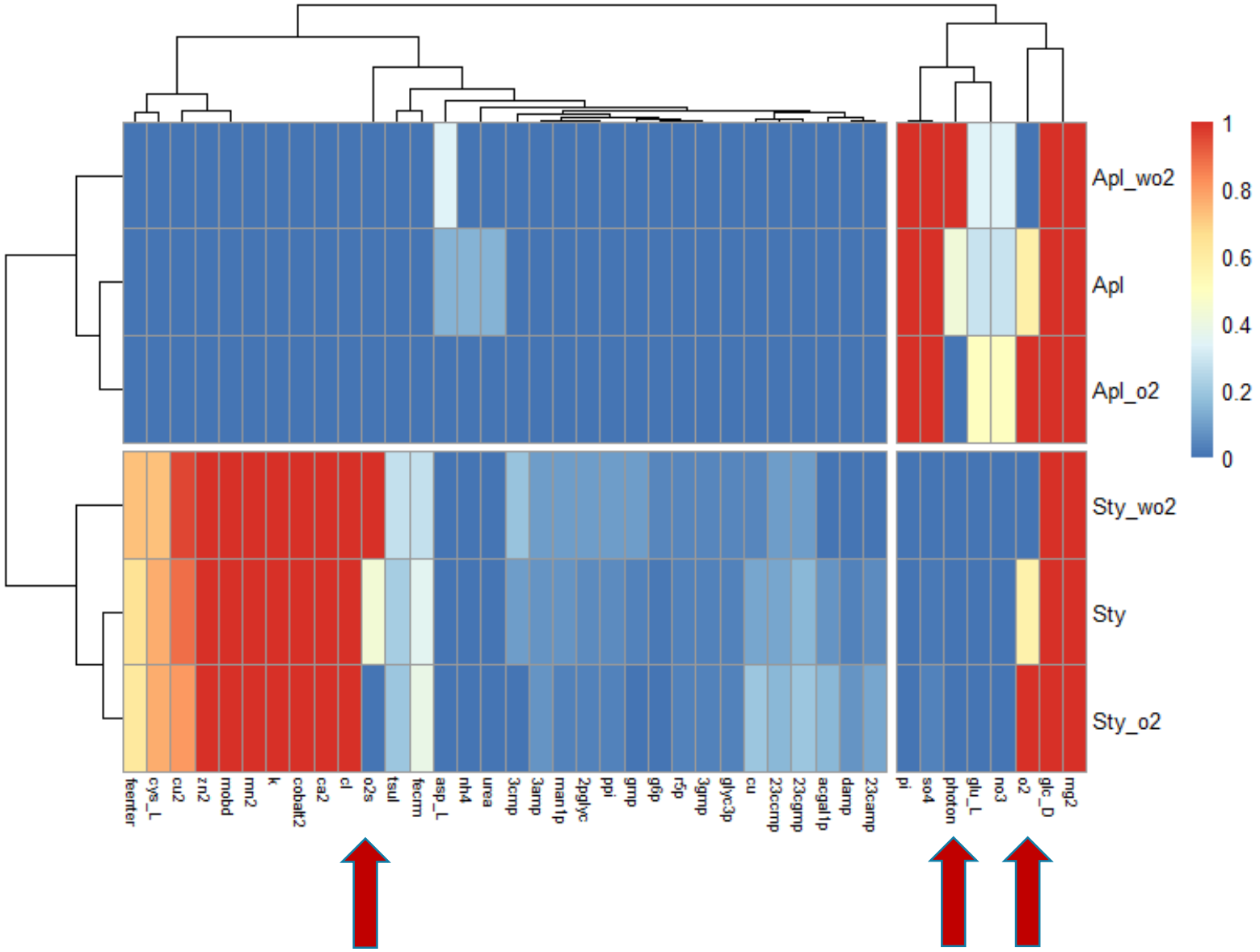
Best Solutions Comparison

All solution with highest score were analyzed

In some cases, O_2 was present in some solutions and absent in others

In the case of *Arthrospira platensis* when O_2 is absent photons are presente (vice-versa)

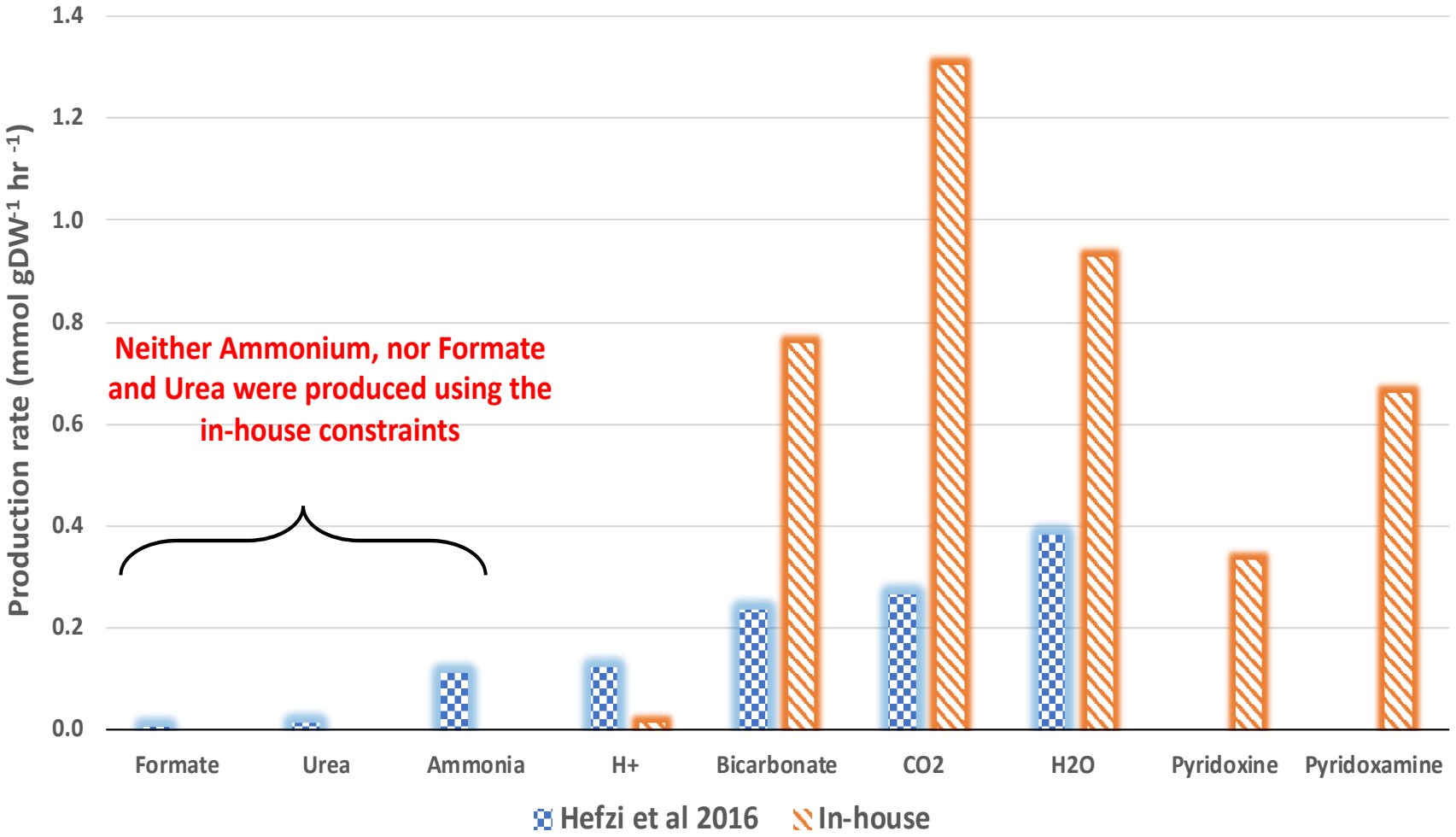
In the case of *Salmonella thyphimurium* when O_2 is absent other oxygen source is presente (O_2S)



Case study

Medium optimization for the production of recombinant protein – CHO cells

Anis Hamdi
(CEB, Portugal and ACIB , Austria)



Metabolites in the medium
Experimental: 33
Optimized: 32

Increased growth yield
up to 3.3 times

Reduce the production of all toxic compound

Results

Microbial Communities

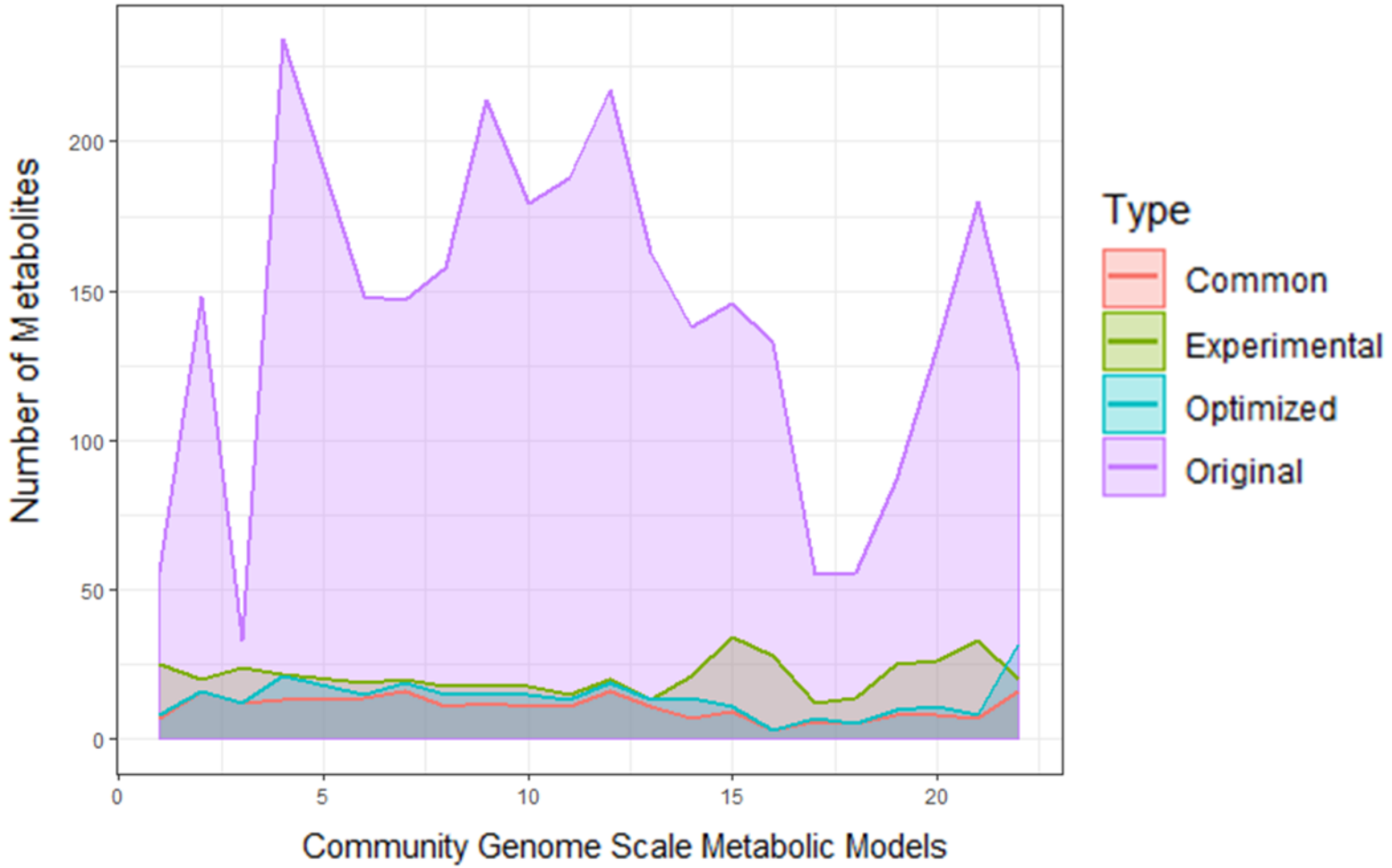
Results

Minimal Medium Composition Comparison

When constructing a community model using FRAMED, all exchange reactions are unconstrained: **Original medium (purple)**

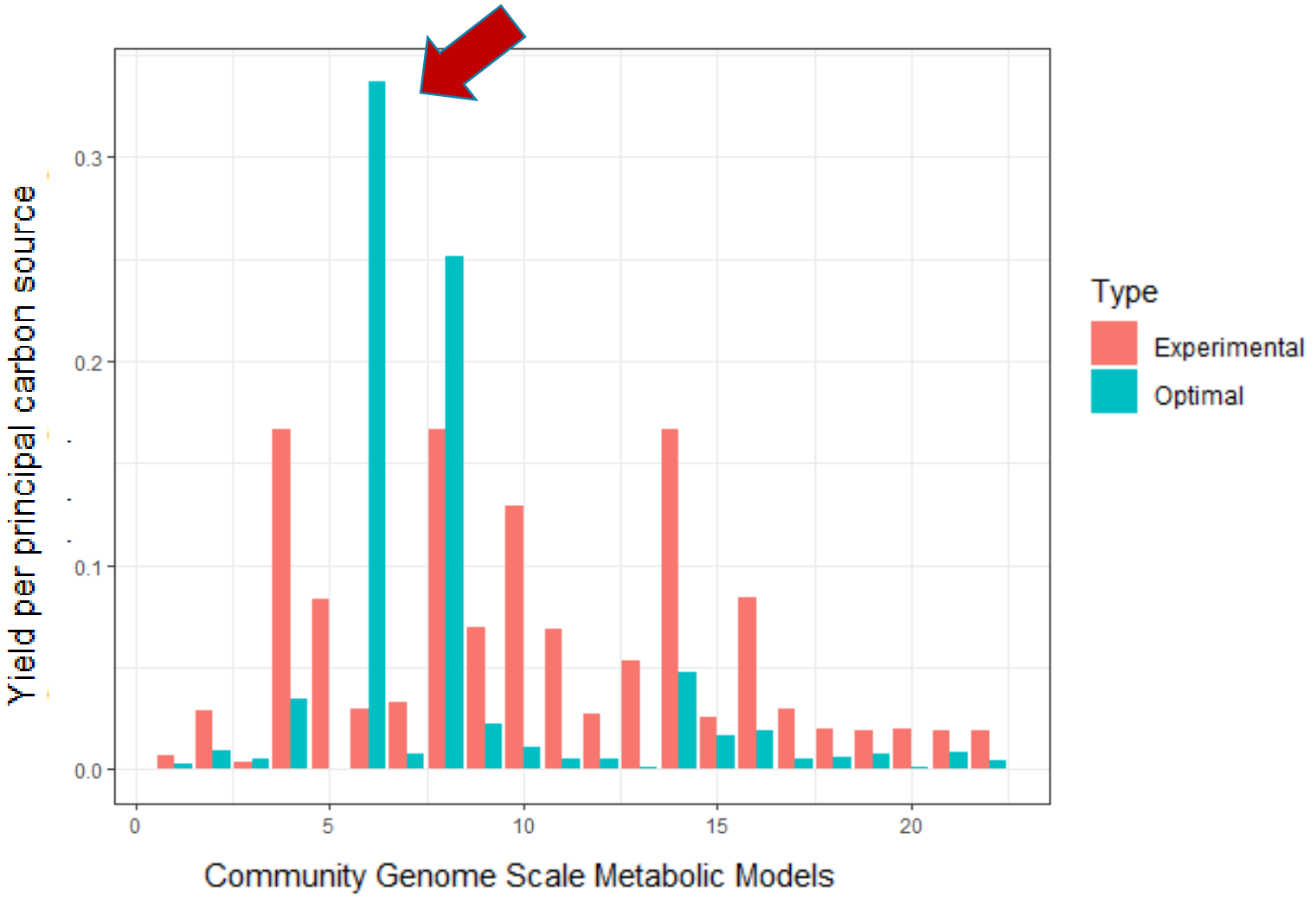
As for single organisms optimized minimal medium **(blue)** is reduced and most of them are in common **(red)** with the original medium.

As for single organisms, differences in the compositions are due to the algorithm selection of different nitrogen, sulfur and/or phosphate sources



Results

Biomass Yield per Carbon Source Comparison



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As for single organisms the biomass yield per principal carbon source is in general lower when optimized minimal medium is used as input

The two exceptions are the microbial communities

Escherichia coli – Corynebacterium glutamicum

Escherichia coli – Pseudomonas putida

Conclusions

- This framework allows to find optimal minimal medium composition in genome-scale metabolic models;
- Results showed biological significance for single organisms and microbial communities;
- Optimization of CHO cells medium has been achieved by increasing growth yield also reducing the production of toxic compounds – experimental validation is being performed;
- Results are promising but further experimental validation has to be made.

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Anis Hamdi

BioSystems Group

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Thank you for your attention.